PEDIATRIC ADVISORY COMMITTEE EXECUTIVE SUMMARY FOR TAMIFLU

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1. INTRODUCTION

Oseltamivir phosphate, hereafter referred to as Tamiflu®, is an ethyl ester pro-drug of a potent and specific inhibitor of the neuraminidase enzyme of influenza virus types A and B. The United States (US) Food and Drug Administration (FDA) approved Tamiflu in 1999 for the treatment of uncomplicated acute illness due to influenza infection in adults and adolescents who have been symptomatic for no more than two days. Tamiflu was also approved by the FDA for treatment of influenza in children aged 1-12 years and for prophylactic use in persons 13 years of age and older in 2000. See Table 2 for Tamiflu approval history in the US, EU and Japan.

Registration of Tamiflu for treatment of influenza in children was granted based on double-blind, randomized, placebo-controlled treatment studies as well as prophylaxis studies and clinical pharmacology studies in 1444 children. Pediatric exclusivity was granted based on these studies, as well as a Phase 3 randomized, open-label study of Tamiflu used for the management of influenza in households. In this study, 353 children aged 1-12 participated. In all studies, the most frequently occurring adverse events were gastrointestinal in nature, occurred early in treatment, were generally single episodes, mild to moderate in nature, and resolved without sequelae. Premature withdrawals from the studies were overall low and equal in the Tamiflu and placebo groups. No clinically meaningful changes in laboratory parameters, vital signs or pulmonary function parameters were observed in otherwise healthy children or those considered at risk with chronic respiratory disease. Overall the safety profile in children aged 1-17 is similar to that seen previously in adult patients.

After pediatric exclusivity was granted in the US in March 2004, the FDA conducted a 13-month review of adverse events in children using Tamiflu from March 22, 2004 until April 22, 2005. During this review, the FDA identified a number of postmarketing safety reports from Japan, including neuropsychiatric events and deaths. Roche performed an analysis of neuropsychiatric serious adverse events reported globally in adults and children and deaths that occurred in children up to age 16 years for Tamiflu from the date of marketing approval until August 15, 2005. Roche has reviewed all of these data as well as all data from a large US health insurance claims database and from all global clinical trials and concluded:

- There have been no new safety signals seen with Tamiflu since registration or pediatric exclusivity were granted.
- There is no disproportion in the rate of deaths in children in Japan compared with the US.
- There is no causal relationship between any of the reported cases of death and the use of Tamiflu. The majority of events occurred in the context of co-morbid conditions and high fever of influenza. In addition, recently reported data from two external groups [1, 2] indicate that Tamiflu use is associated with a reduction in the risk of death across all age groups.
- There is no increase in adverse events for children on Tamiflu versus children with influenza in general.
- There is no causal relationship between Tamiflu and neuropsychiatric events in adults and children and no trend leading to concern about Tamiflu use in children.

2. BACKGROUND ON INFLUENZA

2.1 Incidence of Influenza

Influenza, while usually a self-limiting disease in most individuals, can lead to serious complications. The influenza disease burden is significant in children, with up to 30% of the US pediatric population affected annually. The infection rate in children aged 2-17 years is about twice that for the adult population. Table 1 shows the overall incidence of influenza in Japan and the US by year. Of note, the incidence of influenza in the 2004-2005 season in Japan was about double that in the US.

Table 1 Incidence of Influenza by Season in Japan and the United States

Country	2000–2001	2001–2002	2002–2003	2003–2004	2004–2005
Japan	3.5 million	7.7 million	14.8 million	9.8 million	18 million
United States	11.5 million	10.5 million	6.7 million	10.6 million *	9.4 million

* Note: Early season, most influenza cases occurred in year 2003.

Sources: Japan Vital Statistics, Ministry of Health, Weekly Reports, Infectious Disease Center; US Vital Statistics, CDC, FluStar Surveillance

Hospitalization rates for laboratory-confirmed influenza are higher in young children than in older children. In addition to the significant health risks, discomfort and morbidity caused by the acute illness, children are important to the spread of influenza in the community because of their high viral titers and longer duration of viral shedding, both arising because of the naïve immune system of younger children. This leads to viral persistence and delayed viral clearance. Fatalities and neuropsychiatric events have been described as complications of influenza itself and the estimated rates are discussed below.

2.2 Clinical Manifestations of Influenza

Influenza has most often been described as an illness characterized by the abrupt onset of systemic symptoms such as headache, fever, chills, myalgia, or malaise, and accompanying respiratory tract signs, particularly cough and sore throat. Neurological complications that can occur during influenza infections include confusion, stupor, coma, convulsions and hallucinations. The complications occur in most cases within 8 days after the onset of influenza. Children in particular, may experience febrile convulsions and seizures associated with influenza. Neurological complications are described in more detail below (section 2.3.1). Central nervous system complications of influenza, including encephalitis, transverse myelitis, and Guillain-Barré syndrome, are well documented. Elderly and other high-risk individuals may experience a gradual deterioration of underlying cardiovascular, pulmonary, or renal function subsequent to influenza and these changes occasionally are irreversible and lead to death [3].

2.3 Complications Associated with Influenza Illness

2.3.1 Neurological/Neuropsychiatric Complications

Raised body temperature (fever/hyperthermia), which occurs with influenza, can lead to various consequences such as an increase in metabolic oxygen consumption, heart rate, and respiratory

rate as well as certain neurologic effects. Febrile seizures occur in 2 to 4 percent of young children with high temperatures but are generally benign [4]. Pyrexia can provoke recurrent seizures in up to one third of children who have had febrile seizures. Sleepiness and decreased concentration commonly accompany fever in patients of all ages but may be caused by the central nervous system effects of interleukin-1 rather than by pyrexia itself [5]. Extreme fever or an acute rise in body temperature can cause a change in alertness, confusion, delirium and clouding of consciousness, more commonly in the very young and very old [6]. Neurologic signs, such as mental status changes and seizures, are commonly associated with the acute stages of fever/hyperthermia [7]. Most neurological abnormalities resolve with correction of the underlying disorder and resolution of fever [8]. Many metabolic abnormalities are associated with hyperthermia, including hypoxia, respiratory alkalosis, metabolic acidosis, hypokalemia, hyperkalemia, hypernatremia, hypophosphatemia, hypomagnesemia, and hypoglycemia [9, 10, 11]. These metabolic abnormalities can further lead to neurological abnormalities. Concomitant medications used to treat influenza symptoms can also lead to neuropsychiatric complications.

Nicholson [12] estimated the incidence of febrile convulsions in symptomatic influenza to be between 0.1% and 1% in children under 5 years of age. The association between febrile convulsions in symptomatic influenza was considered to be definitive [13]. The evidence for a possible causal association between influenza and seizures was provided by Van Zeijl et al [14]. They reported a clear association between the yearly peaks of febrile convulsions and the occurrence of influenza A.

Encephalitis/encephalopathy is a well known complication of influenza which is most often reported from Japan [15], where it is reported mainly for children. Some cases of influenza-associated encephalitis/encephalopathy were also observed in the US during the 2003-2004 influenza season [16].

2.3.2 Influenza-Related Mortality

The most common complication of influenza is pneumonia and the mortality of influenza is often expressed as excess deaths caused by pneumonia. In the US, Europe and Japan alone, over 100 million people fall victim to the influenza virus every winter. In the US, studies have confirmed that influenza kills between 10,000 and 40,000 people each year [17, 18]. During the 2003–2004 influenza season there were 143 influenza-related pediatric deaths documented in the US; about 40% of these were children younger than 2 years. Influenza or pneumonia can account for up to 12% of deaths in children [19].

The World Health Organization (WHO), in their Weekly epidemiological record [20] (August 19, 2005), provide the following estimates of hospitalization and deaths due to influenza. In the US, the average excess hospitalization associated with influenza in infants <6 months of age was found to approach 1,000 per 100,000. For previously healthy children <4 years of age, the corresponding average rate was 100 per 100,000 and in the age group 5-15 years, 40 per 100,000. For children at particular risk of serious infection, these annual rates were about 5 times higher than in previously healthy individuals. Whereas the highest infection rates are found in children ages 5-9 years, serious morbidity and mortality from influenza occur more frequently in children aged <2 years, elderly people, and people with high-risk conditions. Very high case-fatality rates are observed among these high risk children <6 months of age.

3. REGULATORY STATUS AND USE OF TAMIFLU

Tamiflu has been approved in over 80 countries worldwide for both treatment and prophylaxis of influenza. The approval dates of Tamiflu in various populations of adults and children in the US, EU, and Japan are shown in Table 2.

Table 2 Tamiflu Approval History

Country	Indication	Population	Approval Date
USA	Treatment of influenza	Adults	October 27, 1999
	Prophylaxis of influenza	Adults and adolescents ≥ 13 years	November 17, 2000
	Treatment of influenza	Patients >1 year old	December 14, 2000
	Prophylaxis of influenza	Patients >1 year old	Pending
EU25 *	Treatment of influenza	Adults and children >1 year	June 20, 2002
	Prophylaxis of influenza	Adult and adolescents ≥ 13 years	June 20, 2002
	Prophylaxis of influenza	Children >1 year	Pending
Japan (capsules)	Treatment of influenza	Adults and adolescents	December 12, 2000
	Treatment of influenza	Children >40 kg	December 24, 2001
	Prophylaxis of influenza	Adults and adolescents	July 9, 2004
Japan (oral suspension)	Treatment of influenza	Adults, adolescents, and children	January 17, 2002

* EU25 includes the following countries: Austria, Belgium, Czech Republic, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, United Kingdom, Iceland, Norway

Patient usage data indicate that prescriptions of Tamiflu for all indications since first approval total about 32 million, with approximately 24 million from Japan and 6 million from the US. Tamiflu usage by year and overall since approval for Japan, the US, and the rest of the world is shown in Table 3.

Table 3 Tamiflu Usage Data — Number of Prescriptions by Year and Country

	Japan	United States	Rest of World
All Ages			
1999 (Nov-Dec)	0	154,518	0
2000	0	744,926	0
2001	487,000	726,548	0
2002	2,138,000	734,775	19,000
2003	7,159,000	1,854,092	380,000
2004	5,721,000	496,664	165,000
2005	8,956,000	1,747,378	387,000
Total 2001-2005	24,461,000	6,458,901	951,000

Data sources:

Japan: IMS Quarterly Rx Data until June 2005

United States: IMS weekly prescriptions until September 2005

Rest of World: IMS MIDAS Quarterly Retail Data (France, Germany, UK, Brazil, Canada, Argentina)

4. OVERVIEW OF DATA SOURCES AND METHODS

In order to evaluate the potential association of Tamiflu to pediatric deaths and neuropsychiatric events across all ages, Roche undertook a careful evaluation of several data sources. These included: (1) global clinical trial database, (2) United Healthcare US database, and (3) Roche global drug safety database. The total numbers of patients and methods used to derive the results are described for each of these sources of data below:

4.1 Clinical Trials Database

The clinical studies included in the Integrated Summary of Safety (ISS) for Tamiflu in the treatment of influenza in children involved 1444 subjects below the age of 18 years of whom 782 were exposed to Tamiflu and 662 to placebo. Most of the subjects included in this ISS (1032) were from two double-blind, randomized, placebo-controlled treatment studies in children ages 1-12 with influenza and in children ages 6-12 with influenza and chronic asthma. Both of these studies included screening and baseline measurements, a 5-day treatment period with Tamiflu 2 mg/kg twice daily, and a post-treatment follow-up period of up to 28 days. Demographic and baseline characteristics were recorded, as were concomitant medications, adverse events, laboratory tests, and vital signs. Adverse events were graded in intensity and according to relationship to treatment.

4.2 United Healthcare Database Studies

4.2.1 US Pediatric Study

As part of good pharmacovigilance practice, Roche contracted with Ingenix corporation to conduct a large retrospective postmarketing study designed to identify potential adverse effects of Tamiflu use in children, with particular focus on skin reactions and on any central nervous system adverse events that could be identified through claims data [21]. The study population was derived from the Ingenix Research Data Mart (RDM), which contains information on over 20 million individuals from 1995 to the present. The database included data both from patients

insured by United Healthcare and from large national employer groups with administrative services provided by United Healthcare. RDM includes medical claims data and pharmacy claims data. Using the RDM, children clinically diagnosed with influenza were identified and were grouped into two cohorts: those with a pharmacy dispensing of Tamiflu on the day of influenza diagnosis (N=8875), and those with influenza diagnosis but no antiviral treatment during the influenza season (N=54,386). The total number of children in the study was 63,261. In each of the two cohorts, the 30 day risk of several skin reactions, adverse drug reactions, anaphylactic shock, loss of consciousness, convulsions, dizziness, depression, and psychotic conditions was examined. Logistic regression was used to compare the risk between cohorts. All diagnoses given to children during the month following influenza diagnosis were identified, classifying the diagnoses by system organ class, and calculating the frequency of each diagnostic category within each of the study cohorts. The events identified in this database were not assessed as serious or non-serious; events were included regardless of the severity of the event. This is a US database study and covered the period of November 1999 to March 2004.

4.2.2 US Study, All Ages

A second retrospective observational cohort study [22] was conducted by Ingenix using the same claims data as above for the same period, but in patients of *all* ages. The study identified 39,202 patients with influenza who received Tamiflu, and 136,799 influenza patients without Tamiflu treatment. The outcomes measured included incidences of claims diagnoses of pneumonia or myocardial infarction, or in-hospital deaths identified in claims. All outcomes were considered potentially influenza-related only if they occurred within 30 days after the influenza diagnosis. Cox proportional hazards models stratified into ten-year age blocks provided hazard ratio estimates for the Tamiflu-exposed group compared to the non-exposed cohort.

4.3 Japanese Retrospective Study, Children < 1 Year

A retrospective surveillance study of Tamiflu was conducted by Chugai pharmaceuticals in Japanese infants less than 1 year of age, who were administered Tamiflu off-label during the influenza season of 2003-2004. The surveillance was conducted in collaboration with four pediatric associations (the Society of Ambulatory and General Pediatrics of Japan, the Japanese Society for Pediatric Infectious Diseases, the Society of Pediatric Fellows of Nagoya City University, and the MHLW Science Research Group “Model Study about the Data Network in Pediatric Drug Therapy”). A total of 834 cases were collected under the surveillance, and 771 of them were found eligible for the safety analysis.

4.4 Roche Global Drug Safety Database

A multiaxial search (using MedDRA version 8.0) of the Roche global safety database was undertaken to identify all reports of deaths, neuropsychiatric and skin serious adverse events for Tamiflu from market approval until August 15, 2005. The database also includes all serious adverse events reported to Chugai (Roche affiliate in Japan), including those spontaneously reported and proactively solicited from physicians in Japan.

The following MedDRA preferred terms were included in the search of neuropsychiatric events:

abnormal behaviour, abnormal dreams, agitation, anxiety, cognitive disorder , completed suicide, confusional state, convulsion, delirium, delusion, delusional perception, depressed level of consciousness, disturbance in attention, encephalitis, encephalopathy, excitability, fear, hallucination, illusion, intentional self-injury, loss of consciousness, mania, , mental impairment, nervousness, panic attack, panic reaction, restlessness, schizophrenia, self injurious behaviour, self mutilation, self-injurious ideation, somatic hallucination, suicidal ideation, suicide attempt, thinking abnormal.

The cases were assessed in regard to temporal relationship of Tamiflu use to the adverse event and confounding factors such as co-medication, medical history and underlying diseases. The cases were categorized into assessment category A, B or C as follows:

A – A plausible causal relationship of Tamiflu use and adverse event exists

B – Alternative explanations or confounders are present which do not allow confirmation of a plausible causal relationship

C – There is insufficient information not allowing a meaningful, reasonable medical interpretation

4.5 Postmarketing Pharmacovigilance in Japan

In Japan, in addition to routine postmarketing safety reporting, an Early Postmarketing Phase Vigilance (EPPV) is required for all new and supplementary new drug applications. An EPPV requires a sponsor to collect adverse reactions for the first six months post launch of a new drug or a new indication. This is done through intensive monitoring and solicited prospective requests by the sponsor to physicians in Japan via Dear Doctor letters. The following table shows all pediatric surveillance programs conducted in Japan regarding Tamiflu.

Table 4 Postmarketing Pediatric Surveillance Programs for Tamiflu in Japan

Name of Survey	Dates Conducted
Survey of pediatrics on dry syrup	Nov 03 – Jul 04
Survey of influenza B patients on Tamiflu capsule	Feb 03 – Aug 05
Retrospective survey in children less than 1 year	Apr 04 – Aug 04*
Prospective survey in children less than 1 year	Jan 05 – Sep 05
EPPV for pediatric prophylaxis	Jul 04 – Mar 05
EPPV of dry syrup	Jul 02 – Mar 03
EPPV of capsule (children over 37.5 kg)	Jul 02 – Mar 03

* Data looked at events from 2001 to 2004.

The solicited events that resulted from the surveillance activities listed in Table 4 are not distinguished from the events reported spontaneously to the sponsor.

5. REVIEW OF DEATHS

Clinical Trial Data

There were no deaths reported during the study period or in the four weeks after the end of the study period among the pediatric or adolescent population (N=1444) in any of the studies conducted.

United Healthcare Database Studies

US study, children ages 1-12 years: During the five influenza seasons covered by this observational study, in over 63,000 children in the US with a diagnosis of influenza, there were no deaths recorded [21].

US study, all ages: In the observational study of over 176,000 patients of all ages with influenza, the risk of death during the 4-week period after influenza diagnosis was 11-fold lower in the Tamiflu-exposed group (1 death in 39,202 patients [0.003%]) compared with the untreated group (56 deaths in 136,799 patients [0.041%]), with a hazard ratio of 0.09 (95% CI of 0.01, 0.65; p = 0.02). These statistically significant findings clearly show that Tamiflu use is associated with a reduced risk of death [22].

Roche Global Drug Safety Data

Thirteen cases of adverse events with an outcome of death were identified from the Roche global drug safety database in children ≤ 16 years. All reported cases originated from Japan. Based upon prescription usage, for children ≤ 16, the reporting rate for death was low in both Japan (1.03 deaths per million prescriptions of Tamiflu) and in the US (0.0 per million) (Table 5) and lower than the mortality rate seen with influenza in general.

Of the 13 deaths in children ≤ 16 reported in Japan, 12 of the deaths were reported from spontaneous/solicited origin, while one case was reported from a postmarketing surveillance study. In none of the 13 deaths was there evidence or plausible explanation of a possible causal relationship to the use of Tamiflu. The majority of events occurred in the context of co-morbid conditions and high fever of influenza, and are consistent with death resulting from complications of influenza. Some cases had insufficient information for evaluation. Based on the analysis of available information, Roche concludes that there is no trend leading to concern about Tamiflu treatment and death. See Appendix 1 for a description of the cases.

Table 5 Number of Deaths per Million Prescriptions of Tamiflu in Children ≤ 16 Years in Japan and the United States

	Total Number of Tamiflu Prescriptions	Events with Outcome Death	Deaths Per Million
Japan			
2001	85,000	1 *	0.00
2002	642,000	4	6.20
2003	4,506,000	2	0.44
2004	2,627,000	2	0.76
2005 (Jan-Jun)	3,754,000	4	1.06
Total 2001-2005	11,614,000	13	1.03
United States			
2001	Data not available	0	0
2002	Data not available	0	0
2003 **	469,343 **	0	0
2004	53,353	0	0
2005 (Jan-Sep)	349,690	0	0
Total 2001-2005	872,386	0	0

* Occurred in the year 2000.

** Patient usage data only available from Oct through Dec by age; however, rate of events is for the entire year.

Note: Patient usage data in the US was provided for ≤ 19 years; however, rate of events is for ≤ 16 years.

6. REVIEW OF SERIOUS NEUROPSYCHIATRIC EVENTS

Clinical Trial Data

In controlled clinical studies with Tamiflu in children below the age of 18 (N=782 for Tamiflu; 662 for placebo), only one serious neuropsychiatric adverse event occurred: viral encephalitis in a patient who received placebo. The incidence in patients receiving Tamiflu was 0/782 (0%).

United Healthcare Database Studies

During the 30 days following an influenza diagnosis in children 1-12 years of age, with the exception of convulsions, all diagnosed occurrences in the nervous sytem occurred with similar frequency in the Tamiflu-exposed and non-Tamiflu-exposed (ie, influenza without Tamiflu) groups. Convulsions occurred at a higher rate in the influenza *without* Tamiflu group (149/54386, 0.3%) than in the influenza with Tamiflu group (12/8875, 0.1%).

Roche Global Drug Safety Data

Table 6 shows the number and reporting rate of neuropsychiatric serious adverse event reports from Japan and the US from marketing approval (1999, US; 2001, Japan) until 2005. The reporting rate in Japan is about 5 per million; in the US the reporting rate is about 3 per million. When reviewed for all ages by year, the rate per million was similar in the US and Japan in 2003 and 2004, but higher in Japan in 2005 (Table 6). For the younger age group, the reporting rates were 6.03 for Japan and 1.15 for the US, likely an artifact of active surveillance of events related to influenza (see Section 7 for discussion).

Table 6 Number of Serious Neuropsychiatric Events per Million Prescriptions of Tamiflu by Year, Age and Country

	Total Number of Tamiflu Prescriptions	Neuropsychiatric Events	Events Per Million
All ages, Japan			
2001	487,000	3	6.16
2002	2,138,000	7	3.27
2003	7,159,000	14	1.95
2004	5,721,000	40	6.99
2005 (Jan-Jun)	8,956,000	58	6.47
Total 2001-2005	24,461,000	122	4.99
All ages, USA			
1999 (Nov-Dec)	154,518	0	0.00
2000	744,926	8	10.74
2001	726,548	1	1.38
2002	734,775	1	1.36
2003	1,854,092	4	2.16
2004	496,664	3	6.04
2005 (Jan-Sep)	1,747,378	2	1.14
Total 2001-2005	6,458,901	19	2.94
≤ 16 years, Japan			
2001	85,000	1	11.76
2002	642,000	4	6.23
2003	4,506,000	9	1.99
2004	2,627,000	25	9.51
2005 (Jan-Jun)	3,754,000	31	8.25
Total 2001-2005	11,614,000	70	6.03
≤ 19 years, USA *			
1999	Data not available	0	0
2000	Data not available	0	0
2001	Data not available	0	0
2002	Data not available	0	0
2003 (Oct-Dec) **	469,343 **	1 **	2.13
2004	53,353	0	0
2005 (Jan-Sep)	349,690	0	0
Total 2001-2005	872,386	1	1.15

* Patient usage data in the US was provided for ≤ 19 years; however, rate of events is for ≤ 16 years.

** Patient usage data only available for Oct through Dec by age; however, rate of events is for the entire year.

Of the total cases of events reported from all countries, 46% occurred in children up to 16 years of age. When the events occurring in children up to 16 years of age were broken down by groups based on similar symptoms and pathophysiology, the following results were obtained:

Group 1 – Hallucination, hallucination auditory, hallucination visual, hallucinations mixed, delusion, delusional perception: 13 cases – one from Germany, 12 from Japan. All were spontaneous/solicited reports. All had alternative explanations of causality (category B)

Group 2 – Loss of consciousness, depressed level of consciousness: 15 cases – all Japan, all spontaneous/solicited, 12 had alternative explanations (category B), 2 insufficient info (category C), and in 1 case a plausible explanation for causal role was possible (category A)

Group 3 – Convulsion, encephalitis, encephalopathy: 19 cases – 18 Japan, 1 US; 16 spontaneous/solicited reports, 3 from studies; 17 had alternative explanations (category B), 2 insufficient info (category C)

Group 4 – Delirium: 10 cases – all Japan; 9 spontaneous/solicited, 1 study; 9 had alternative explanations (category B), 1 insufficient info (category C)

Group 5 – Abnormal behavior, agitation, anxiety, confusional state, excitability, mania, mental impairment, panic reaction, restlessness, schizophrenia: 10 cases – all Japan, all spontaneous/solicited, 8 had alternative explanations (category B), 1 insufficient info (category C), 1 category A

Of all events (adults and children), in all but two cases there were possible alternative explanations for the neuropsychiatric event or confounders such as previous use of hallucinogenic and illicit drug, alcoholism, history of cerebral hemorrhage, depression, anxiety, cerebral infarction, hypertension, transient ischemic attack, etc. Fever and dehydration due to influenza as a cause for inducing neurological, psychiatric or neuropsychiatric symptoms must be considered. In only two cases there was positive rechallenge and dechallenge with Tamiflu: in one case the events were depressed level of consciousness and abnormal behavior in an 8-year-old male, and in the second case the event was abnormal behavior in another 8-year-old male.

The majority of the events (80%) occurred within 5 days after starting Tamiflu. This also coincides with the severity of influenza symptoms such as high fever, dehydration, secondary complications, etc., indicating again that most events had confounding factors. The majority of the events (96%) were spontaneous reports or from solicited reports in Japan. There are important limitations to consider when using spontaneously reported adverse event information, including difficulties with event recognition and report quality [23]. Spontaneously reported information is uncontrolled and therefore subject to the possible influence of a number of biases that can affect reporting, including the length of time a product has been on the market, country, reporting environment, detailing time, and quality of the data [24].

Based on the analysis of available information, Roche concludes that there is no trend leading to concern for neuropsychiatric events with Tamiflu treatment.

7. DISCUSSION OF EVENT RATE IN JAPAN VERSUS THE UNITED STATES

Influenza is experienced by millions of people each year and Tamiflu use is estimated to be over 33 million worldwide since first approval. Neurological complications are not uncommon during influenza infections, the symptoms of which occur concurrently with the usage of Tamiflu, making any causal relationship of these events to Tamiflu difficult to assess in the absence of a controlled trial. In the placebo-controlled trials and US Healthcare database studies, which had a control group, no deaths occurred with Tamiflu and there were no serious adverse events, including neuropsychiatric events, that cause concern with Tamiflu use.

Prescription data indicate that Tamiflu use in Japan has been four times higher than Tamiflu use in the US, about 24 million vs 6 million since approval. As a result, deaths and neuropsychiatric events were evaluated as a *rate* (number of events per million prescriptions of Tamiflu). The Roche global drug safety database showed the rates of deaths per million prescriptions of Tamiflu were low and similar in Japan and the US for children ≤ 16 years. In addition, the reported deaths from Japan in children are not above the expected rates seen for influenza associated mortality. As described in the retrospective US cohort study in adults and children, Tamiflu use is associated with an 11-fold decrease in mortality due to influenza in the US [22]. In a recent publication from Sugaya et al (2005) [30], the authors noted a decrease in influenza associated mortality among young Japanese children and postulate that the decrease is due to both an increase in the vaccination rate and widespread use of neuraminidase inhibitors. Tamiflu therefore may have a beneficial effect on the mortality rate overall.

For serious neuropsychiatric events in all ages, there was a higher reporting rate of events per million prescriptions of Tamiflu in Japan vs the US for all years combined and in 2005, but similar rates per million between countries in 2003 and 2004. There are several factors that may be contributing to both the higher number and type of events being reported from Japan, especially in 2005. These include: (1) increased marketing promotion in Japan (2) surveillance differences between the US and Japan; (3) differences in Tamiflu dosing and delivery; and (4) differences in treatment practice and reporting of events between Japan and the US. Each of these factors is discussed below:

Social and Health Promotion in Japan

Via broadcasts on television and radio, the Ministry of Health, Labor, and Welfare in Japan recommended that patients visit a hospital or clinic when they suspect influenza upon having fever and fatigue. Due to increased awareness on television and through sales representative visits to physicians regarding Tamiflu, it was prescribed to a higher than usual number of patients in clinics and hospitals when they developed influenza in the 2004-2005 season.

Surveillance Differences

The approval in Japan of Tamiflu for prophylaxis in adults and adolescents in July 2004 triggered an early postmarketing phase vigilance (EPPV) period. In addition, the EPPV period coincided with the very active 2004-2005 influenza season in Japan: about 18 million patients with influenza with the majority of these patients receiving Tamiflu. In addition, reports were solicited from 70,000 physicians and their reports are included in the spontaneous postmarketing

reports of adverse events. This combination of active solicitation of events and an active influenza season likely contributed to the higher number of reports from Japan in 2005.

As part of good pharmacovigilance practice, Roche contracted with Ingenix corporation to analyze data from a large healthcare database in the US [21]. The study investigated the safety of Tamiflu in over 63,000 children with influenza aged 1-12 years who were members of a health insurance claims database. There was no indication of an increased risk of neuropsychiatric events for children aged 1-12 over that already posed by influenza illness alone.

Differences in Tamiflu Dosing and Delivery

Several differences related to Tamiflu use in Japanese children may also play a role in the adverse events reported. These differences include:

- *Duration of Tamiflu treatment:* Although the label in Japan specifies treatment for 5 days, information from Chugai, Roche's marketing affiliate in Japan, is that more often, treatment duration is determined by resolution of fever and in practice is typically only 2, 3 or 4 days. This could be responsible for recrudescence, which in turn may help explain some of the events reported. In 2003, leading physicians in Japan began recommending a shorter administration period for Tamiflu (3 days), a practice which may be persisting to this day [28]. According to a study by Yamaura and Yoshihara, when a shorter Tamiflu treatment period was compared with the 5-day course of treatment, results suggested that the 2-day treatment was significantly high in reconsultation rate and the 5-day treatment was significantly high in medication dispensing fee. Therefore, the 3-day treatment with Tamiflu was concluded to be the most suitable from the standpoint of clinical effect combined with economics [29].

- *Tamiflu delivery:* Tamiflu powder for oral suspension for children is dispensed by pharmacists in Japan as a powder in individual sachets, rather than as a suspension or capsule; several of these sachets are prepared at the pharmacy level for each patient. Use in this manner has not been studied by Roche and it is not known what the impact may be on actual exposure.

- *Tamiflu use off-label:* Despite being approved for children 1 year and older, substantial off-label use in children < 1 year of age has been reported in Japan. This prompted Chugai Pharmaceuticals, Roche's marketing affiliate in Japan, to conduct a retrospective surveillance study of children <1 year who received Tamiflu during the influenza season of 2003-2004. This study was conducted in collaboration with four pediatric associations. Safety data from 771 children <1 year were reviewed showing that the overall incidence of adverse drug reactions and adverse events was low in this population (3.2% and 5.3%, respectively). The types of events were similar to those reported in older children during clinical trials and in practice post-approval. These data indicate that no new safety signals were observed in children <1 year. A prospective safety surveillance study intended to collect adverse events in children <1 year of age has recently been completed. The results and report for this study are in progress.

Treatment Practice and Reporting Differences

Medical practice in Japan differs from the US in several important ways with respect to Tamiflu use and influenza. According to information provided by Chugai Pharmaceuticals, a very small proportion of physicians in Japan (less than 4%) specialize in either pediatrics or infectious diseases. As a result, many physicians may not have a lot of experience in distinguishing between complications of influenza illness itself, and Tamiflu-related events. To address this, during the 2004-2005 influenza season Chugai prepared and disseminated educational materials on influenza [25, 26, 27]. Most of the neuropsychiatric events in Japan were reported by general practitioners and a psychiatric evaluation was not performed. The majority of events reported in Japan occurred in the context of co-morbid conditions and high fever of influenza. This reporting difference may, in some way, be responsible for both the type and number of events reported in Japan.

8. CONCLUSIONS

Based on epidemiological data on influenza itself and on large database studies, there is no increase in deaths or neuropsychiatric events for patients on Tamiflu versus patients with influenza in general. With regard to deaths, the reported rates are low in both Japan (1.03 per million) and the US (0.0 per million) for children ≤ 16 years and lower than the mortality rates seen with influenza in general.

Regarding neuropsychiatric symptoms, influenza symptoms such as high fever and dehydration, as well as secondary complications, typically occur within the early course of the disease, which coincides with the administration of Tamiflu. So although there was a higher rate of neuropsychiatric events reported in Japan, primarily during a severe early-2005 flu season, the majority of these events occurred within five days of starting Tamiflu, and hence were not surprising, given the symptoms caused by influenza itself. A number of factors in Japan could account for the apparent higher rate of events reported in the year 2005, the most likely being the intensive monitoring of adverse events in the six months after the launch of Tamiflu for prophylaxis of influenza and the active solicitation of adverse events, which coincided with a very active 2004-2005 influenza season. There are also important differences in medical practice, social and health promotion in Japan, and Tamiflu dosing and delivery which may play a role.

Finally, data from a cohort study conducted in 63,000 children with an influenza diagnosis in the US demonstrated no increased neuropsychiatric risk with Tamiflu use. In fact, recently reported data indicate that Tamiflu use is associated with an 11-fold decrease in influenza-associated mortality in patients in the US [22] and among young children in Japan [30].

Based on analyses of all available information, Roche has concluded that there is no association between Tamiflu use and the deaths or neuropsychiatric events reported. Roche sees no scientific or medical basis for any changes in how Tamiflu is used.

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Appendix 1 Death Cases

Age	Gender	(DRSN) Indication (Preferred Term)	(DRSN-THSN) Tamiflu Total Daily Dosage	(DRSN) Days from Start of Tamiflu and Death Date	(DRSN) Co-medication INN Generic Name	(AESN) Serious Adverse Event Preferred Term (Event Type) ***** = Events with Outcome Death	(DRSN-AESN) Latency	(MHSN) Medical History	Comments after case review
3	M	1) Influenza	1-1) 25 mg	1) 47 days	2) Diclofenac (S) 3) Amantadine (N) 4) Cefazolin Sodium (N) 5) Diazepam (N) 6) Phenytoin Sodium (N) 7) Fructose/Glycerol (N) 8) Dexamethasone Sodium Phosphate (N) 9) Panthenol (N) 10) Mannitol (N)	1) Pneumonia (AE) ***** 2) Encephalopathy (AE) 3) Brain Oedema (AE) 4) Subarachnoid Haemorrhage (AE) 5) Renal Failure (AE)	1-1) -1 day 1-2) -1 day 1-3) -1 day 1-4) 5 days 1-5) -1 day		Pt. had onset of pneumonia, renal failure, cerebral oedema and encephalopathy one day prior to start of oseltamivir. The pt. died 47 days after the first dose of oseltamivir, due to complications of influenza.
5	F	1) Drug Use For Unknown Indication	1-1) 150 mg	1) Unknown	2) Ketotifen (S) 3) Cromoglicic Acid (S) 4) Cefdinir (S)	1) Injury Asphyxiation (AE) *****	1-1) 1 day	1) Asthma 2) Influenza	The oseltamvir dose seems high based on the patient's age (weight not provided). Pt. had a history of asthma and died due to asphyxiation. Aspiration of sputum and vomit is suspected.
2	M	1) Influenza	1-1) 50 mg	1) 0 days	2) Cyproheptadine (S) 3) Tipepidine (N) 4) Bromhexine (N)	1) Sudden Death (AE) *****	1-1) 0 days	1) Varicella 2) Influenza	Myocarditis further to influenza was considered as a probabale cause of death. He also had respiratory difficulties and went into cardiac arrest and could not be resuscitated.

Age	Gender	(DRSN) Indication (Preferred Term)	(DRSN-THSN) Tamiflu Total Daily Dosage	(DRSN) Days from Start of Tamiflu and Death Date	(DRSN) Co-medication INN Generic Name	(AESN) Serious Adverse Event Preferred Term (Event Type) ***** = Events with Outcome Death	(DRSN-AESN) Latency	(MHSN) Medical History	Comments after case review
9	M	1) Influenza	1-1) 79 mg	1) 5 days	2) Glucose (N) 3) Generic Component(S) Unknown (N) 4) Sodium Bicarbonate (N) 5) Cromoglicic Acid Or Famotidine (N) 6) Epoetin Beta (N) 7) Carbocisteine (N) 8) Metronidazole (N) 9) Lactobacillus Acidophilus (N) 10) Tilactase (N) 11) Sodium Bicarbonate (N)	1) Pancreatitis Acute (AE) *****	1-1) 4 days	1) Acidosis 2) Influenza 3) Cerebral Palsy 4) Renal Impairment 5) Inborn Error Of Metabolism 6) Mental Retardation Severity Unspecified	The cause of death was reported as acute pancreatitis. (Lab values: C-reactive protein – 0.74 mg/dl, Amylase – 1209, Alkaline phosphatase – 350, creatine kinase – 1502, LDH – 1362, SGOT – 874, SGPT – 343 – units not provided). A history of methylmalonic acidosis is a confounder and might have led to acute pancreatitis. The pt. also has a history of renal impairment, inborn errors of metabolism and cerebral palsy.
0.67	M	1) Influenza	1-1) 18 mg	1) 57 days	2) Furosemide (N) 3) Furosemide (N) 4) Spironolactone (N) 5) Beraprost Sodium (N) 6) Carbocisteine (N) 7) Procaterol (N) 8) Cyproheptadine (N) 9) Generic Component(S) Unknown (N) 10) Salbutamol Sulfate (N) 11) Cefmetazole (N) 12) Cefazolin Sodium/Lidocaine Hydrochloride (N) 13) Midazolam (N) 14) Dopamine (N)	1) Respiratory Failure (AE) *****	1-1) 0 days	1) Influenza 2) Trisomy 21 3) Pneumonia 4) Ventricular Septal Defect	The pt. died due to respiratory failure (a complication of influenza). History of congenital ventricular septal defect is a confounder. The case is from post-marketing surveillance study # ML18272.

Age	Gender	(DRSN) Indication (Preferred Term)	(DRSN-THSN) Tamiflu Total Daily Dosage	(DRSN) Days from Start of Tamiflu and Death Date	(DRSN) Co-medication INN Generic Name	(AESN) Serious Adverse Event Preferred Term (Event Type) ***** = Events with Outcome Death	(DRSN-AESN) Latency	(MHSN) Medical History	Comments after case review
3	M	1) Influenza	1-1) Unknown	1) Unknown		1) Sudden Death (AE) *****		1) Influenza	Reported in a Japanese newspaper with lack of information - dose, latency, co-medications. Autopsy results are not available although autopsy was performed.
2	M	1) Influenza	1-1) Unknown	1) Unknown		1) Sudden Death (AE) *****		1) Asthma 2) Influenza	Reported in a Japanese newspaper with lack of information - dose, latency, co-medications. Autopsy results are not available although autopsy was performed.
2	M	1) Influenza	1-1) Unknown	1) Unknown		1) Sudden Death (AE) *****		1) Influenza	Reported in a Japanese newspaper with lack of information - dose, latency, co-medications. Autopsy results - brain oedema and pulmonary oedema
3	M	1) Influenza	1-1) Unknown	1) Unknown		1) Sudden Death (AE) *****		1) Asthma 2) Influenza	Reported in a Japanese newspaper with lack of information - dose, latency, co-medications. Autopsy results - cerebellar tonsillar herniation and pulmonary oedema
4	F	1) Influenza	1-1) 2 gram	1) 1 day	2) Paracetamol (N) 3) Cyproheptadine (N) 4) Ambroxol Hydrochloride (N)	1) Sudden Death (AE) *****	1-1) 1 day	1) Influenza 2) Bronchitis	Pt. has a history of asthma. Myocarditis secondary to influenza is a suspected cause of death. The reported dose of 2 grams is high.

Age	Gender	(DRSN) Indication (Preferred Term)	(DRSN-THSN) Tamiflu Total Daily Dosage	(DRSN) Days from Start of Tamiflu and Death Date	(DRSN) Co-medication INN Generic Name	(AESN) Serious Adverse Event Preferred Term (Event Type) ***** = Events with Outcome Death	(DRSN-AESN) Latency	(MHSN) Medical History	Comments after case review
2	M	1) Influenza	1-1) 18 mg 1-2) 36 mg 1-3) 18 mg	1) 85 days	2) Phenobarbital (N)	1) Cardio-Respiratory Arrest (AE) ***** 3) Cardiac Failure Acute (AE) 4) Pulmonary Oedema (AE) 5) Brain Oedema (AE)	1-1) 3 days 1-3) 1 day 1-4) 3 days 1-5) 3 days	1) Influenza 2) Hydrocephalus 3) Meningocele 4) Arnold-Chiari Malformation 5) Epilepsy 6) Meningeomas Surgery 7) Ventriculoperitoneal Shunt Malfunction	Pt. developed brain oedema, pulmonary oedema, acute cardiac failure and cardio-respiratory arrest 3 days after starting oseltamivir. He was successfully resuscitated, but died later on an unknown date. Medical history of CNS disease is a confounder.
4	M	1) Influenza	1-1) 64.2 mg	1) 62 days	2) Paracetamol (N) 3) Tulobuterol (N) 4) Tipepidine (N) 5) Cyproheptadine (N)	1) Chest Pain (AE) ***** 2) Death (AE) *****	1-1) 2 days 1-2) 1 day	1) Influenza	Pt. had difficulty in breathing and developed cardio-respiratory arrest, and died 2 days after the start of oseltamivir. An autopsy was not performed.
14	M	1) Influenza	1-1) 75 mg	1) 0 days		1) Depressed Level Of Consciousness (AE) *****	1-1) 0 days	1) Influenza	Two hours after the ingestion of one capsule of oseltamivir the patient fell out of a window of his apartment on 9th floor and died of hemorrhagic shock. It was not clear if this was a suicide or an accident (possibly due to clouding of consciousness). An autopsy was not performed. Medical history and co-medications are lacking. Insufficient information does not permit assessment.